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Short communication

Complications of herpes zoster in immunocompetent older adults: Incidence in vaccine and placebo groups in two large phase 3 trials

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ABSTRACT

Background: An adjuvanted herpes zoster (HZ) subunit vaccine, HZ/su, demonstrated high efficacy against HZ and postherpetic neuralgia (PHN) in two randomized, observer-blind, placebo-controlled trials in adults aged ≥50 and ≥70 years (ZOE-50 and ZOE-70, respectively).
Methods: Data from ZOE-50 and ZOE-70 trials were analyzed to evaluate the efficacy of HZ/su against mortality, hospitalizations, and non-PHN complications of HZ including HZ-associated vasculitis, stroke, and disseminated, ophthalmic, neurologic, and visceral diseases.
Results: In the pooled ZOE-50/ZOE-70 analysis, 1 of 32 HZ/su recipients (3.1%) and 16 of 477 placebo recipients (3.4%) with a confirmed HZ episode had complications other than PHN. Efficacy against HZ-related complications was 93.7% (95% confidence interval, 59.5–99.9%) in adults aged ≥50 years and 91.6% (43.3–99.8%) in adults ≥70 years. Five HZ-related hospitalizations, all in placebo recipients, and no HZ-related deaths were reported.
Conclusions: HZ/su reduces the risk of HZ-associated complications in older adults (NCT01165177; NCT01165229).

1. Introduction

Herpes zoster (HZ) results from the reactivation of latent varicella-zoster virus (VZV) in sensory ganglia, typically years after primary infection [1,2]. The most common complication of HZ, postherpetic neuralgia (PHN), is a chronic neuropathic pain that persists after resolution of the HZ rash [2,3]. In adults aged ≥50 years, the risk of developing PHN can be >30% [4]. Other HZ complications include disseminated HZ, and neurological, visceral, or vascular diseases, including stroke [1,4–6]. HZ ophthalmicus occurs when VZV reactivation affects the ophthalmic branch of the fifth cranial nerve and can involve eye structures (hereafter referred to as ophthalmic disease) [7]. The risk of HZ ophthalmicus among HZ patients ranges between 10% and 15%, with ophthalmic disease in approximately 30–80% of these cases [4,8]. The incidence, severity, and duration of PHN and other HZ complications generally increase with age [4].

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In two phase 3 clinical trials, a HZ subunit vaccine (HZ/su), containing recombinant VZV glycoprotein E and the $AS01_B$ Adjuvant System, was highly efficacious in preventing HZ and PHN in older adults [9,10]. Here, we report the efficacy of HZ/su in preventing HZ-associated complications, hospitalizations, and deaths.

2. Methods

2.1. Study design and participants

ZOE-50 (Clinicaltrials.gov, NCT01165177) and ZOE-70 (NCT01165229) were randomized, observer-blind, placebo-controlled, phase 3 studies conducted concurrently in 18 countries in Europe, North America, Latin America, and Asia-Australia [9,10]. Adults aged ≥50 years (ZOE-50) or ≥70 years (ZOE-70) received two doses of HZ/su (Shingrix, GSK) or placebo intramuscularly at months 0 and 2. The design and results of both studies have been previously published [9,10].

2.2. Study objectives

The primary objectives were to assess HZ/su efficacy against HZ (ZOE-50 and ZOE-70) and PHN (ZOE-70) [9,10]. The secondary and exploratory objectives of each study described here included HZ/su efficacy in reducing HZ-associated complications and efficacy in reducing HZ-related mortality and hospitalizations.

2.3. Assessment of HZ and PHN cases

Subject-reported suspected HZ cases were confirmed by polymerase chain reaction or by an ascertainment committee, as previously described [9,10]. PHN was defined as a 'worst pain' score ≥3 persisting or developing more than 90 days after the onset of HZ rash, based on item #3 of the Zoster Brief Pain Inventory questionnaire [10,11].

2.4. Herpes zoster complications

The following complications of suspected HZ cases were recorded by the investigators as adverse events or serious adverse events, as appropriate: HZ vasculitis; disseminated HZ; ophthalmic, neurologic, or visceral disease; and stroke (definitions in Table 1). In the analysis, these events were considered complications of HZ only if they were associated with a confirmed HZ case.

2.5. Statistical analysis

All analyses were performed in the modified vaccinated cohort [9,10], which excluded participants who did not receive the second dose or who had a confirmed HZ episode within 30 days after the second dose.

In both studies, the incidence of HZ-associated complications in participants with confirmed HZ (overall and by age group) was compared between HZ/su and placebo recipients using the asymptotic standardized unconditional binomial test [12]. The analysis was stratified by age group and weighted according to the proportion of participants in each age group. Efficacy against HZ-related mortality and hospitalizations considered the exact inference on the relative risk stratified for age groups and regions, conditionally to the total number of confirmed HZ cases observed and time at risk. This method computes an exact confidence interval (CI) around the rate ratio (ratio of the event rates in the HZ/su versus placebo group) and takes into account the follow-up duration of the subjects within each group. Vaccine efficacy was defined as 1 minus the rate ratio. HZ/su efficacy against HZ-associated complications or against mortality and hospitalizations was demonstrated if the lower limit of the two-sided 95% CI was greater than 0%.

The low number of confirmed HZ cases in the HZ/su group in each study limited the power of the analyses. Therefore, a post-hoc analysis was performed to assess efficacy in reducing the incidence of HZ-associated complications (exclusive and inclusive of PHN) in the combined ZOE-50/ZOE-70 study population, both for participants aged ≥50 years and ≥70 years.

All significance tests were two-tailed. P-values of ≤0.05 were considered to indicate statistical significance. All statistical analyses were performed using SAS version 9.3 (SAS Institute) and StatXact 9.0 (Cytel) procedure for SAS.

3. Results

3.1. Study population

ZOE-50 and ZOE-70 enrolled 15,411 and 13,900 evaluable participants, respectively [9,10]. Since publication of the primary results of ZOE-50 (which was ongoing at the time of publication [9]), 47 additional participants had HZ episodes: 3 in the HZ/su group and 44 in the placebo group. Therefore, during the entire ZOE-50 study period (mean follow-up, 3.9 ± 0.7 years), 263 subjects had a confirmed HZ episode: 9 in the HZ/su group and 254 in the placebo group. In ZOE-70 (mean follow-up, 3.7 ± 0.8 years),

Table 1
Definition of herpes zoster complications.

HZ complication	Definition
Disseminated disease	Defined as ≥6 HZ lesions outside the primary dermatome as per the investigator's judgment
Ophthalmic disease	Defined as HZ affecting any eye structure as per investigator's judgment
Neurologic disease	Defined as cranial or peripheral nerve palsies, myelitis, meningoencephalitis, stroke, etc. that was temporally associated with an episode of HZ and, in the opinion of the investigator, directly caused by VZV infection arising from the HZ episode
Visceral disease	Defined as an abnormality of one or more internal organs (e.g., hepatitis, pneumonitis, gastroenteritis) temporally associated with an episode of HZ and, in the opinion of the investigator, directly caused by VZV infection arising from the HZ episode
HZ vasculitis	Vasculopathy or vasculitis (based on clinical, laboratory, or radiologic findings) that was temporally associated with an episode of HZ and, in the opinion of the investigator, directly caused by VZV infection arising from the HZ episode
Stroke	A diagnosis of stroke required that criteria 1, 2, and 3 or criteria 1 and 4 were fulfilled, and in the opinion of the investigator was temporally associated with an episode of HZ Criterion 1: Rapid onset of localizing neurological deficit and/or change in level of consciousness Criterion 2: Localizing neurological deficit or change in level of consciousness that lasted greater than 24 h Criterion 3: No other cerebral process, peripheral lesion, or other disorder is the cause of the localizing neurological deficit or change in level of consciousness Criterion 4: CT or MRI scan evidence of an acute thrombotic or hemorrhagic lesion

CT, computed tomography; HZ, herpes zoster; MRI, magnetic resonance imaging; VZV, varicella-zoster virus.

246 participants had a confirmed HZ episode: 23 in the HZ/su group and 223 in the placebo group [10].

3.2. HZ/su efficacy against HZ-related complications other than PHN

In the overall ZOE-50/ZOE-70 combined population, only one HZ-related complication, ophthalmic disease, was observed among the 32 HZ/su recipients (3.1%) with confirmed HZ (Table 2). At least one HZ-related complication other than PHN was reported in 16 out of 477 (3.4%) placebo recipients with a confirmed HZ episode. The most frequently reported complication in the placebo group was ophthalmic disease (seven participants [1.5%]), followed by disseminated disease (six participants [1.2%]), neurologic disease (three participants [0.6%]), and one case of vasculitis presumed to be due to HZ (0.2%). One participant had both ophthalmic and neurologic (meningitis) disease. Most HZ-related complications occurred in participants ≥70 years (13/17; 76.5%). No cases of HZ-associated visceral disease or stroke were reported in participants in either the HZ/su group or placebo group. All participants with HZ-related complications received antiviral therapy (usually within the first 3 days after onset) and most received pain medication.

Excluding PHN, the HZ complication rate for placebo recipients ≥50 years was 0.3/1000 person-years (PY) overall and increased with age (Table 3). HZ/su reduced the risk of HZ-related complications other than PHN by 93.7% (95% CI, 59.5–99.9%; P = 0.0003) in participants ≥50 years and by 91.6% (95% CI, 43.3–99.8%; P = 0.0035) in participants ≥70 years.

3.3. HZ/su efficacy against HZ-related complications including PHN

In the ZOE-50/ZOE-70 combined population ≥50 years with confirmed HZ, PHN and other complications developed in 5 of 32 HZ/su recipients and in 58 of 477 placebo recipients (Table S1). HZ/su reduced HZ-related complications including PHN by 91.3% (95% CI, 78.5–97.3%; P < 0.0001) in participants ≥50 years and by 88.6% (95% CI, 71.2–96.5%; P < 0.0001) in those ≥70 years.

3.4. Reduction of mortality and hospitalizations related to a confirmed HZ episode

In ZOE-50, no deaths or hospitalizations related to a HZ episode were reported. In ZOE-70, no HZ-related deaths or hospitalizations were reported for participants who received HZ/su, whereas five HZ-related hospitalizations were reported in participants who received placebo (Table S2). These were for neurologic disease (two participants), disseminated HZ (one participant), neurologic and ophthalmic disease (one participant), and reaction to codeine given for HZ pain relief (one participant). HZ/su efficacy

Table 2
HZ-related complications (other than PHN) in participants with a confirmed HZ episode in the ZOE-50/ZOE-70 pooled population (modified vaccinated cohort)*

Complications	HZ/su (N = 13,881)			Placebo (N = 14,035)		
	Number of participants with a confirmed HZ episode	Participants with at least one specified HZ-related complication[a]		Number of participants with a confirmed HZ episode	Participants with at least one specified HZ-related complication[a]	
		n	%		n	%
Ophthalmic disease						
50–59 years	4	0	0.0	103	0	0.0
60–69 years	3	0	0.0	90	1	1.1
70–79 years	19	1	5.3	216	4	1.9
≥80 years	6	0	0.0	68	2	2.9
Overall	32	1	3.1	477	7	1.5
Disseminated disease						
50–59 years	4	0	0.0	103	1	1.0
60–69 years	3	0	0.0	90	1	1.1
70–79 years	19	0	0.0	216	2	0.9
≥80 years	6	0	0.0	68	2	2.9
Overall	32	0	0.0	477	6	1.3
Neurologic disease						
50–59 years	4	0	0.0	103	0	0.0
60–69 years	3	0	0.0	90	0	0.0
70–79 years	19	0	0.0	216	3	1.4
≥80 years	6	0	0.0	68	0	0.0
Overall	32	0	0.0	477	3	0.6
HZ vasculitis						
50–59 years	4	0	0.0	103	0	0.0
60–69 years	3	0	0.0	90	1	1.1
70–79 years	19	0	0.0	216	0	0.0
≥80 years	6	0	0.0	68	0	0.0
Overall	32	0	0.0	477	1	0.2
Subjects with at least one HZ-related complication						
50–59 years	4	0 (0)	0.0	103	1 (1)	1.0
60–69 years	3	0 (0)	0.0	90	3 (3)	3.3
70–79 years	19	1 (1)	5.3	216	8 (9)	3.7
≥80 years	6	0 (0)	0.0	68	4 (4)	5.9
Overall	32	1 (1)	3.1	477	16 (17)	3.4

HZ, herpes zoster; HZ/su, herpes zoster subunit vaccine; PHN, postherpetic neuralgia.
No cases of visceral disease or stroke were diagnosed in participants with a confirmed HZ episode. Therefore, these categories are not shown in this table.
* The modified vaccinated cohort excluded participants who did not receive the second dose of the herpes zoster subunit vaccine (HZ/su) or placebo or who had a confirmed episode of herpes zoster within 1 month (30 days) after the second dose.
[a] All confirmed HZ episodes considered. Numbers in parentheses represent the number of HZ-related complications.

Table 3
HZ/su efficacy against HZ-related complications (other than PHN) in the ZOE-50/ZOE-70 pooled population (modified vaccinated cohort).

Participants	HZ/su				Placebo				Vaccine efficacy		
	Number of participants	Number. of participants with HZ-related complications	Cumulative follow-up period (year)[a]	Rate of HZ complications (per 1000 person-years)	Number of participants	Number. of participants with HZ-related complications	Cumulative follow-up period (year)[a]	Rate of HZ complications (per 1000 person-years)	%[b]	95% CI	P-value
By age group											
50–59 years	3491	0	13,789.7	0.0	3523	1	13,941.4	0.1	100.0	−3890.4; 100.0	1.0000
60–69 years	2140	0	8621.4	0.0	2166	3	8671.8	0.3	100.0	−142.8; 100.0	0.2513
70–79 years	6468	1	24,437.4	0.0	6554	8	24,691.4	0.3	87.4	5.9; 99.8	0.0403
≥80 years	1782	0	6324.4	0.0	1792	4	6277.5	0.6	100.0	−51.1; 100.0	0.1245
Total population											
≥70 years	8250	1	30,761.7	0.0	8346	12	30,968.9	0.4	91.6	43.3; 99.8	0.0035
Overall (≥50 years)	13,881	1	53,172.9	0.0	14,035	16	53,582.1	0.3	93.7	59.5; 99.9	0.0003

CI, confidence interval; HZ, herpes zoster; HZ/su, herpes zoster subunit vaccine; PHN, postherpetic neuralgia.
[a] Censored at the first occurrence of a confirmed HZ-related complication other than PHN.
[b] Vaccine efficacy was calculated by means of the Poisson method. Vaccine efficacy in each age group was adjusted for region and overall vaccine efficacy was adjusted for age group and region. P-values were two-sided exact P-values conditional to the number of cases.

against HZ-related mortality or hospitalization was 100% (95% CI, −9.9–100.0%; P = 0.0636).

4. Discussion

Based on the ZOE-50/ZOE-70 pooled analysis, HZ/su efficacy against HZ-related complications other than PHN was 93.7% in participants aged ≥50 years and 91.6% in those ≥70 years. These results are consistent with the overall efficacy against HZ, which was 97.2% (95% CI, 93.7–99.0%) in adults aged ≥50 years (ZOE-50) [9] and 91.3% (95% CI, 86.8–94.5%) in adults aged ≥70 years (ZOE-50/ZOE-70) [10]. This indicates that efficacy against complications other than PHN was largely driven by the prevention of HZ in HZ/su recipients. Because the number of breakthrough HZ cases in the HZ/su vaccinated group was small, even in the pooled population, it is not possible to determine whether HZ/su prevented complications in vaccine recipients with breakthrough HZ. Similarly, in the ZOE-70 trial, fewer hospitalizations were seen in the HZ/su group than in the placebo group but the difference was not statistically significant due to the low numbers of events in both groups. However, a limitation of our study is that some of these analyses are post-hoc.

The large cohort of placebo recipients in these trials provided robust estimates of the incidence of HZ complications, without the biases inherent in population-based estimates from databases and case series. Excluding PHN, the overall complication rate for placebo recipients ≥50 years was low at 0.3/1000 PY. This represents a HZ complication rate of 3% among participants with confirmed HZ. The most common complications were ophthalmic (1.5%), disseminated (1.2%) and neurologic (0.6%) diseases. When PHN was included as a complication, the complication rate was 11%. The age-specific incidence of PHN and other HZ-related complications was less common among placebo recipients in our studies than in previous studies [4,13,14]. This may be partly attributable to the enrolment of only immunocompetent individuals into our trials. In addition, as HZ episodes were closely monitored during the trials, a relatively high proportion of participants with HZ likely received prompt antiviral therapy [1,2], which may have reduced the rate of complications and hospitalizations.

In the pooled analysis, efficacy against HZ-related complications was similar in adults aged ≥50 years and ≥70 years, indicating that efficacy did not decline with age. This was true whether or not PHN was included in the analysis and consistent with the overall efficacy against HZ previously described [9,10]. In conclusion, our results indicate that vaccination with two doses of HZ/su substantially reduces the overall risk of HZ-associated complications among adults ≥50 years.

Trademark statement

Shingrix is a trademark of the GSK group of companies.

Contributions

AC, RJ, ML, and AV contributed to the data collection, data interpretation, and writing of the manuscript. LC contributed to the data analysis, data interpretation, and writing of the manuscript. MK, HL, and TH contributed to the study design, data analysis, data interpretation, and writing of the manuscript. All authors read and approved the final manuscript. GSK takes a commitment to convey a message in a way that would be easily understandable by health care professionals (Supplementary text).

Conflicts of interest

MK and LC are employees, and TH and HL former employees, of the GSK group of companies (GSK). MK and HL hold shares or stock options in GSK as part of their current or former employee remuneration. HL is a current employee of Pfizer and receives stock as part of his employee remuneration. TH is a consultant for GSK and is the co-inventor of a patent application related to the vaccine used in this study. AC and AV declare that their institution received a grant from GSK for the conduct of the clinical trial. AC received honoraria paid to his institution from GSK, Merck, and Sequirus. RJ received honoraria for consultancy and funding for a meeting he organized from Merck, funding from Sanofi Pasteur MSD to organize a scientific meeting, and honoraria as a consultant for GSK. ML received grants from GSK and Merck Sharp & Dohme, participated to advisory boards sponsored by GSK and Merck Sharp & Dohme, and received royalties for a zoster vaccine patent owned by Merck Sharp & Dohme. AV received honoraria for the participation to an advisory board for Sanofi Pasteur MSD and an adjudication committee for Watermark.

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All authors attest they meet the ICMJE criteria for authorship.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2018.02.029.

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